Nitrio oxide, bytochrome c and mitochondria.

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Nitric oxide (NO) and its derivative, peroxynitrite (ONOO-), inhibit mitochandrial respiration, and this inhibition may contribute to both the physiological and dytotoxic actions of NO. Manomolar concentrations of NO rapidly and reversibly inhibited cytochrome oxidase in competition with oxygen, as shown with isolated cytochrome oxidase, mitochendria, brain herve terminals and cells. Cultured astrocytes and macrophages activated (by cytokines and endotoxin) to express the inducible form of NO synthase produced up to 1 microM NO, and inhibited their own respiration and that of co-incubated cells via reversible NO inhibition of dytochrome oxidase. NO-induced inhibition of respiration in brain nerve terminals resulted in rapid glutamate release, which might contribute to the neurotoxisity of NO. NO inhibition of cytochrome oxidase is reversible; however, incubation of cells with NO donors for 4 nours resulted in an inhibition of complex I, which was reversible by light and thiol reagents and may be due to nitrosylation of thiols in complex I. NO also caused the acute innibition of catalase, stimulation of hydrogen peroxide production by mitochondria, and reaction with hydrogen peroxide on superoxide dismutase to produce peroxynitrite. Peroxynitrite inhibited complexes I, II and V (the ATP synthase), abonitase, breatine kinase, and increases the proton leak in isolated mutochondria. Peroxymitrite also caused opening of the permeability transition pore, resulting in the release of cytochrome c, which might then trigger apoptosis. Hypoxia/ischaemia also resulted in an acute reversible inhibition of cytochrome oxidase. Heart ischaemia baused the release of cytochrome o from mitochondria into the bytosol, and at the same time daspase-3-like-protease activity was activated in the cytoplasm. Addition of cytochrome c to non-ischaemic cytosol also caused activation of this protease activity, suggesting that caspase activation and consequent apoptosis is at least partly a result of this cytochrome a release.

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